

**Amendments to the Specification:**

Please replace the paragraph beginning at page 4, line 4 with the following rewritten paragraph:

From these observations and other observations, the involvement of at least two different G-proteins, one involved in PLC and  $\text{Ca}^{2+}$  activation ( $G_P$ ) and one directly regulating exocytosis ( $G_E$ ), has been suggested (Gomperts et al., 1991; reviewed by Sagi-Eisenberg 1993). Indeed, it was subsequently demonstrated that basic secretagogues induce histamine secretion by interacting directly with  $G_E$ , a pertussis toxin-sensitive heterotrimeric G protein, in a receptor-independent manner (Aridor et al., 1990; Aridor & Sagi-Eisenberg 1990). This G-protein was subsequently identified as  $G_{i3}$ , which appears to mediate the peptidergic pathway leading to exocytosis in mast cells. In particular, a synthetic peptide which corresponds to the C terminal sequence of  $G_{\alpha i3}$  (KNNLKECGLY, SEQ ID NO:1) was able to inhibit histamine release when introduced, into permeabilized mast cells (Aridor et al., 1993).

Please replace the paragraph beginning at page 4, line 19 with the following rewritten paragraph:

One approach is based on the fusion of the selected peptide with a specific hydrophobic sequence, comprising the "h" region of a signal peptide sequence. Examples of such hydrophobic regions are the signal sequence of the Kaposi fibroblast growth factor (AAVALLPAVLLALLAP, SEQ ID NO:3; Lin et al., 1995) and the signal sequence within human integrin  $\beta_3$  (VTVLALGALAGVGVG, SEQ ID NO:4; reviewed by Hawiger 1997). Another approach is based on fusing the active anti-allergic peptide with a specific signal peptide sequence endowed with the membrane translocation properties of the homeodomain of Antennapedia, a *Drosophila* transcription factor (RQPKIWFPNRRKPWKK, SEQ ID NO:5; Prochiantz 1996).

Please replace the paragraph beginning at page 7, line 4 with the following rewritten paragraph:

According to a preferred embodiment of the present invention, the linker is a covalent bond. Preferably, the covalent bond is a peptide bond. More preferably, the molecule is a peptide taken from the C terminal sequence of  $G_{\alpha i3}$ . Most preferably, the peptide has an amino acid sequence AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:7).

Please replace the paragraph beginning at page 7, line 8 with the following rewritten paragraph:

According to another particularly preferred embodiment of the present invention, the molecule is a peptide having an amino acid sequence AAVALLPAVLLALLAPKENLKDCGLF (SEQ ID NO:12).

Please replace the paragraph beginning at page 8, line 2 with the following rewritten paragraph:

According to currently more preferred embodiment of the present invention, the molecule comprises a peptide having an amino acid sequence selected from the group consisting of:

- i) AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:7) ;
  - ii) AAVALLPAVLLALLAPKENLKDCGLF (SEQ ID NO:12) ;
  - iii) Succinyl- AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:8) ;
  - iv) Cyclic- AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:9) ;
- and mixtures, functional homologs or derivatives thereof.

Please replace the paragraph beginning at page 8, line 22 with the following rewritten paragraph:

(a) attaching a leader sequence to the molecule, the leader sequence being a peptide having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:3), to form a complex; (b) administering the complex to the subject; and (c) importing the complex into the cell through the leader sequence, such that the molecule is imported into the cell.

Please replace the paragraph beginning at page 10, line 17 with the following rewritten paragraph:

Figure 11: A computerized model demonstrating 3D structure of the C- terminus sequence of Peptide 2-KNNLKECGLY, SEQ ID NO:1 (A) and peptide 5m-KNNLKDCGLF, SEQ ID NO:2 (B).

Please replace the paragraph beginning at page 13, line 7 with the following rewritten paragraph:

According to the principles of the present invention, novel peptides, designated as peptides 1-6, were designed and synthesized to include distinct importation competent signal peptides as a first segment at the N-terminus (underlined) and the C-terminal sequences of  $\text{G}\alpha\text{i}_3$  or  $\text{G}\alpha\text{i}_t$  at the C-terminus as a second segment. In the following list the non-underlined part is  $\text{G}\alpha\text{i}_3$  for peptides 1-3, and  $\text{G}\alpha\text{i}_t$  for peptides 4-6:

1. VTVLALGALAGVGVGKNNLKECGLY (SEQ ID NO:6)
2. AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:7)
3. RQPKIWFPNRRKPWKKKNNLKECGLY (SEQ ID NO:10)
4. VTVLALGALAGVGVGKENLKDCGLF (SEQ ID NO:11)
5. AAVALLPAVLLALLAPKE NLKDCGLF (SEQ ID NO:12)
6. RQPKIWFPNRRKPWKKKENLKDCGLF (SEQ ID NO:13)

Please replace the paragraph beginning at page 17, line 8 with the following rewritten paragraph:

As demonstrated in Figure 1, peptides 1 and 4 (which both include the leader motif of the signal sequence within human integrin  $\beta_3$  linked to the C-terminal sequences of  $\text{G}\alpha\text{i}_3$  or  $\text{G}\alpha\text{i}_t$ , respectively) exerted hardly any stimulatory effect on histamine secretion at a concentration range of up to 400  $\mu\text{g}/\text{ml}$  of the peptide (Figure 1A). Similar results were obtained with peptides 2 and 5 (which both include the leader motif of the signal sequence of the Kaposi fibroblast growth factor linked to the C-terminal sequences of  $\text{G}\alpha\text{i}_3$  or  $\text{G}\alpha\text{i}_t$ , respectively) at a concentration range of up to 600  $\mu\text{g}/\text{ml}$  of the peptide (Figure 1B). In contrast, peptides 3 and 6 (which both include the leader motif of the homeodomain of a *Drosophila* transcription factor linked to the C-terminal sequences of  $\text{G}\alpha\text{i}_3$  or  $\text{G}\alpha\text{i}_t$ , respectively) induced histamine secretion from mast cells in a concentration dependent manner (Figure 1C). These results suggest that peptides containing the h region of a signal peptide sequence of either the signal sequence of the Kaposi fibroblast growth factor or the signal sequence within human integrin  $\beta_3$ , can serve as potential inhibitors of mast ~~cells~~ cells exocytosis, as they do not exert side effects of effecting histamine secretion. In contrast, peptides including the leader motif of the homeodomain of the *Drosophila* transcription factor induce side effects of histamine secretion, and therefore can not serve as potential inhibitors of mast ~~cells~~ cells exocytosis.

Please replace the paragraph beginning at page 20, line 17 with the following rewritten paragraph:

The first such mutation is a point mutation in peptide 5. Specifically, in peptide 5, the glutamic acid in position 18 was replaced by asparagine, to form peptide 5-modified (Peptide 5m AAVALLPAVLLALLAPKNNLKDCGLF, SEQ ID NO:14). In this peptide the last 10 amino acids are homologous to the C-terminal sequence of Gai<sub>2</sub>.

Please replace the paragraph beginning at page 20, line 21 with the following rewritten paragraph:

N-terminus of the peptides 2 and 5, to form 2 new sequences:

Peptide 12: KAAVALLPAVLLALLAPKNNLKDCGLF (SEQ ID NO:16)

Peptide 13: KAAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:17)

Please replace the paragraph beginning at page 21, line 1 with the following rewritten paragraph:

Amino acids were then deleted, in order to shorten peptides 2 and 5, by removing 3 amino acids from positions 17-19 to form 2 new sequences, respectively:

Peptide 20: AAVALLPAVLLALLAPLKECGLY (SEQ ID NO:18)

Peptide 21: AAVALLPAVLLALLAPLKDCGLF (SEQ ID NO:19)

Please replace the paragraph beginning at page 21, line 5 with the following rewritten paragraph:

Also, various point mutations were made in peptide 2. First, cysteine residue was replaced, in an attempt to improve peptide efficacy and to avoid possible oxidation of the peptide. Specifically, the cysteine residue in position 23 of peptide 2 was replaced by serine, to form the following sequence:

Peptide 25: AAVALLPAVLLALLAPKNNLKESGLY (SEQ ID NO:20)

Please replace the paragraph beginning at page 21, line 10 with the following rewritten paragraph:

An additional approach to improve peptide solubility involved changing the configuration of the peptide N-terminus to D/L configuration, thus forming the sequence:

Peptide 2 D/L: H- (D, L)-A- (D, L)-A-VALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:21)

Please replace the paragraph beginning at page 21, line 13 with the following rewritten paragraph:

Also, in order to improve peptide solubility, a succinyl residue was added to the N-terminus of the peptides, to form 2 new sequences :

Peptide 2-Succinylated (2-Suc):

Succinyl-AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:8)

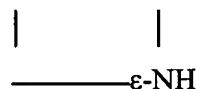
Peptide 5-Succinylated (5-Suc):

Succinyl-AAVALLPAVLLALLAPKENLKDCGLF (SEQ ID NO:15)

Please replace the paragraph beginning at page 24, line 20 with the following rewritten paragraph:

In light of the aforementioned results, a cyclic form of peptide 2 was synthesized, forming a cyclization between the side chain of Lysine at position 17 and the C-terminus of the peptide:

Peptide 2-Cyclic (2-Cyc): AAVALLPAVLLALLAPKNNLKECGLY-CO (SEQ ID NO:9)



Please replace Table 1 at page 26 with the following rewritten Table 1:

Peptide	Sequence	Secretagogue*	Inhibitor**	Remarks
2	AAVALLPAVLLALLAPKNNLKECGLY ( <u>SEQ ID NO:7</u> )	-	++	Intermediate Solubility
-2Suc	Succinyl-AAVALLPAVLLALLAPKNNLKECGLY ( <u>SEQ ID NO:8</u> )	-	+++	Good solubility
-2Cyc	AAVALLPAVLLALLAPKNNLKECGLY $\begin{array}{c}   \quad   \\ \text{-----}\epsilon\text{-NH} \end{array}$ ( <u>SEQ ID NO:9</u> )	-/+	+	Poor solubility
5	AAVALLPAVLLALLAPKENLKDCGLF	-	++	Intermediate

	(SEQ ID NO:12)			Solubility
5m	AAVALLPAVLLALLAPKNNLKDCGLF (SEQ ID NO:14)	+	-	
-5Suc	Succinyl- AAVALLPAVLLALLAPKENLKDCGLF (SEQ ID NO:15)	+	-	
12	KAVALLPVLLALLAPKNNLKDCGLF (SEQ ID NO:16)	+	-	
13	KAVALLPVLLALLAPKNNLKECGLY (SEQ ID NO:17)	+	-	
20	AAVALLPAVLLALLAPLKECGLY (SEQ ID NO:18)	-	-	
21	AAVALLPAVLLALLAPLKDCGLF (SEQ ID NO:19)	-/+	-	
25	AAVALLPAVLLALLAPKNNLKESGLY (SEQ ID NO:20)	+	-	
2 D/L	H- (D, L)-A- (D, L)-A VALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:21)	+	-	

Please replace Table 3B at page 30 with the following rewritten Table 3B:

**B: Effect of Peptide on 48/80 induced wheal ~~wel~~ response**

Peptide application Animal	Peptide concentration		
	0	1 mg/ ml	10 mg/ ml
A	41.0	41.4	9.2
B**	42.4	39.8	19.1

Please replace Table 5B at page 30 with the following rewritten Table 5B:

**B: Effect of Peptide on compound 48/80 induced wheal ~~wel~~ response**

Peptide concentration Animal	0	1 mg/ ml	10 mg/ ml
A <sup>*</sup>	112. 8	75.7	21.3
B <sup>**</sup>	63.1	1.6	5.3
C <sup>***</sup>	56.8	41.2	15

Please replace the paragraph beginning at page 36, line 10 with the following rewritten paragraph:

Hereinafter, the term "subject" refers to the human or lower animal to whom the therapeutic agent is administered. For example, administration may be done topically (including ~~ophthalmically~~ ophthalmically, vaginally, rectally, intranasally and by inhalation), orally, or parenterally, for example by intravenous drip or intraperitoneal, subcutaneous, or intramuscular injection.

Please replace the paragraph beginning at page 38, line 16 with the following rewritten paragraph:

According to another preferred embodiment of the present invention, a peptide could optionally be modified. For example, the N-terminus of the peptide could be modified by ~~succinilation~~ succinylation, addition of a sugar residue, or addition of stearic or palmitic acid. In addition, certain amino acids of the peptide could also be modified. For example, if the peptide includes a cysteine at amino acid 23, this cysteine could be replaced by another amino acid, including but not limited to, amino butyric acid, serine or other such amino acids. As another example, if the peptide includes a lysine at amino acid 17, this residue could be replaced by another amino acid, such as a neutral amino acid, or two amino acids such as a pair of glutamic acid residues. As yet another example, if the peptide includes a proline at amino acid 16, this residue could be replaced by another amino acid, such as a neutral amino acid, or two amino acids such as a pair of glutamic acid residues. Thus, the peptide could optionally be modified in order to enhance penetration into the cell or to enhance the pharmaceutical activity, for example.